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Sequential Changes in the Metabolic Response in Severely Septic Patients During the First 23 Days After the Onset of Peritonitis

Lindsay D. Plank, DPhil, Andrew B. Connolly, MB, ChB, and Graham L. Hill, MD

From the University Department of Surgery, Auckland Hospital, Auckland, New Zealand

Objective
To quantify the sequential changes in metabolic response occurring in patients with severe sepsis after the onset of peritonitis.

Summary Background Data
Understanding the changes in energy expenditure and body composition is essential for the optimal management of severely septic patients; however, they have not been quantified in the context of modern surgical care.

Methods
Twelve patients with severe sepsis secondary to peritonitis (median APACHE II score = 21.5) had measurements of energy expenditure and body composition as soon as they were hemodynamically stable and 5, 10, and 21 days later. Sequential measurements of acute-phase proteins and cytokine responses were also made.

Results
Resting energy expenditure rose to 49% above predicted and remained elevated throughout the study period. Total energy expenditure was 1.25 × resting energy expenditure. Body fat was oxidized when energy intake was insufficient to achieve energy balance. There was a positive fluid balance of 12.5 l over the first 2 days after onset of sepsis; thereafter, body water changes closely paralleled body weight changes and were largely accounted for by changes in extracellular water. During the 21-day study period, there was a loss of 1.21 kg (13%) of total body protein. During the first 10 days, 67% of the protein lost came from skeletal muscle, but after this time it was predominantly from viscera. Intracellular potassium levels were low but did not deteriorate further after hemodynamic stability had been reached. There was a reprioritization of hepatic protein synthesis that was obligatory and independent of changes in total body protein. The cytokine responses demonstrated the complexity, redundancy, and overlap of mediators.

Conclusions
The period of hypermetabolism in severely septic patients is similar to that previously described, but the fluid changes are larger and the protein loss is greater. Protein loss early on is predominantly from muscle, thereafter from viscera. Fat loss can be prevented and cell function preserved once hemodynamic stability is achieved.

Patients with severe sepsis demonstrate a characteristic picture in which hypermetabolism occurs, protein and fat are consumed, and body water and salt are conserved.[1] These fundamental changes lie at the heart of present management of the severely septic patient; however, many of the changes described have not been quantified in the context of modern surgical care. The availability of body composition methodology, which has been adapted for use in critically ill patients in intensive care,[2] enabled us to quantify the sequential changes in the metabolic response that occurred in a group of severely septic surgical patients.

METHODS

Patients

A series of patients with severe sepsis secondary to perforation of an abdominal viscus were enrolled in this study after referral by the intensivists of the Auckland Hospital Department of Critical Care Medicine (DCCM). The criteria for the diagnosis of severe sepsis were those of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) consensus statement.[3]

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Address reprint requests to Professor Graham L. Hill, University Department of Surgery, Fifth Floor, Auckland Hospital, Private Bag 92024, Park Road, Auckland 3, New Zealand.
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The study was approved by the North Health Ethics Committee, and informed consent was obtained from each patient, or usually the patient's next of kin.

Clinical Management

For each patient, diagnosis was made on clinical grounds (acute onset of agonizing pain, prostration, development of systemic sepsis and physical signs of peritonitis), and after immediate resuscitation and the administration of broad-spectrum antibiotics, the patient was transferred to the surgical suite for definitive surgery (Table 1) and extensive peritoneal toilet. After surgery, the patients were transferred to the DCCM, where they were managed in consensus fashion by a group of five full-time intensivists, according to standard clinical guidelines and a series of protocols.[4] Patients were nursed at a 1:1 ratio by specialist intensive care nurses. Patients were ventilated to normoxemia and normocarbia, and positive end-expiratory pressure was limited to 15 cm H_2O or less, unless required for alveolar flooding or hypoxemia despite an FiO_2 >0.8.[4] Patients were sedated with morphine infusions, with pancuronium and intermittent diazepam added when neuromuscular blockade was desired.[5] Tracheostomy (surgical or percutaneous)[4,6] was often performed before ventilatory weaning.

Circulatory resuscitation was guided by clinical assessment, including continuous monitoring of thoracic compliance, pulse oximetry, intraarterial blood pressure, electrocardiography, and core temperature in every patient. Blood volume expansion was with crystalloid and colloid (4% albumin or fresh-frozen plasma), and transfusion of packed red cells was used to keep the hematocrit between 0.3 and 0.4. All patients had inotropic support with dopamine and, in the majority of patients, noradrenaline.[7] Some patients received infusions of adrenaline, dobutamine, milrinone, phenylephrine, or angiotensin.[8] All patients without contraindications received digoxin.[9] Amiodarone[10] and DC cardioversion were used to control cardiac rhythm when required. Pulmonary artery catheters were placed only if shock, respiratory failure, and renal function were simultaneously worsening. Resuscitation was considered optimal when the mean arterial pressure was 90 to 110 mmHg, the heart rate was 80 to 120 (in sinus rhythm), acid–base status was normal, and hourly urine output was >2 ml/kg.

Antibiotics were given according to a predetermined protocol and were modified if specific microbiologic information became available. No patient received selective decontamination of the gut, nonsteroidal antiinflammatories, or steroids. Only patients with blood found on nasogastric aspiration were given sucralfate; famotidine was used instead if there was massive gastric fluid loss.

Nutrition was given enterally (Osmolite, Ross Laboratories, Columbus, OH) when possible.[11] Enteral intake was increased up to 1.3 × the measured resting energy expenditure (REE) according to a standard protocol and continued until at least 1000 kcal from oral food could be tolerated. Patients with contraindications to enteral feeding, or in whom a trial of enteral nutrition failed, were given intravenous nutrition by dedicated single-lumen central venous catheters.[12] The initial daily prescription of 17 g nitrogen, 1000 kcal from glucose, and 1000 kcal from fat was modified on the basis of size, renal function, and indirect calorimetry.

Patients were transferred from the DCCM when endotracheal intubation, ventilatory support (including continuous positive airway pressure), and titrated inotropic support were no longer required. Tracheostomy, hemodialysis, intravenous nutrition, or low-dose dopamine infusion did not preclude ward care, but patients receiving several such therapies at once often remained in intensive care.

Study Design

Patients underwent serial measurements of energy expenditure, plasma protein concentrations, and body composition during a period of 21 days. Cytokine concentrations were measured at enrollment and at 8, 24, 48, 72, and 96 hours later. Measurements of cytokine concentrations were also made on days 7 and 12 after the onset of sepsis. The other studies were performed as soon as hemodynamic stability was achieved without either colloid infusion or increasing inotropic support (study day 0) and were repeated 5, 10, and 21 days later (Fig. 1). The body composition measurements were performed in the Department of Surgery in a facility specially designed for studying critically ill patients.[13] Patients received all necessary intensive therapy during the 4-hour study periods.

Energy Measurements

Measured Energy Expenditure

Oxygen consumption and carbon dioxide production were measured twice daily, in accordance with the procedures detailed elsewhere,[14] between 8 AM and 10 AM and 4 PM and 6 PM, beginning as soon as possible after DCCM admission and continuing at least through study day 10 and again on study day 21. The average REE[15,16] was calculated from these two measurements, as described previously.[14]

Predicted Energy Expenditure

For each patient, a value of predicted REE was calculated on the day of each body composition study using the Harris–Benedict equations.[17]

Energy Balance

The construction of energy balance is described in detail elsewhere.[18] An energy balance for the time between each pair of body composition measurements was calculated from changes (Δ) in measured components of body composition (total body fat [TBF], total body protein [TBP], and total body glycogen) according to the following equation:

Table 1. CLINICAL DATA OF 12 PATIENTS WITH PERITONITIS WHO UNDERWENT SEQUENTIAL METABOLIC STUDIES OVER A 21-DAY PERIOD

Patient	Sex	Age (yrs)	Apache II	Septic Source & Etiology	Comorbidity	Surgical Procedures*	Clinical Events*	Outcome*	Prescan (Days)†	Ventilated (Days)	Inotropic Support‡	Days in DCCM	Days in Hospital
A	M	70	30	Peritonitis due to perforated obstructed jejunum	Ileostomy (Ulcerative colitis with past total colectomy)	Laparotomy, small bowel resection and primary anastomosis (0) MM for HIAP (0) Laparotomy, washout, and reduction of MM (4, 11, 15) Tracheostomy (12) Evacuation of hematoma (16)	HIAP (0) Recurrent SVT ARF (4) Small bowel fistula (15) Abdominal hematoma (16)	Death (24)	2	24	1,2	24	29
B	M	61	34	Peritonitis due to perforated duodenal ulcer	Alcholism	Laparotomy, omental patch (0) Tracheostomy (8) Repair of dehiscence (11) Feeding jejunostomy placed (11)	Alcohol withdrawal (−1) Diazepam overdose (0) Aspiration pneumonitis (0) Shock (0) AF with rapid ventricular response (0) VF arrest (1) ARF (1) Wound dehiscence (11)	Survivor	3	10	1,2	13	34
C	F	51	17	Peritonitis due to perforated appendicitis	Newly-diagnosed IDDM	Laparotomy, appendicectomy (0)	Shock (0) ARF (0)	Survivor	1	4	1,2	6	30
D	M	59	26	Peritonitis due to ruptured urachal fungal abscess	NIDDM Hypercholesterolaemia	Laparotomy, biopsy of urachal mass, repair of bladder dome (0) Cystoscopy, evacuation of bladder hematoma (7) Embolization of vesical arteries (8)	Shock (0) ARF (0) *S. pyogenes wound infection (4)* Hematuria (5) *E. faecalis* CVL sepsis (13)	Survivor	3	8	1,2	15	25

E	F	70	22	Peritonitis due to gallstone ileus with small bowel perforation	Nil	Laparotomy, small bowel resection, repair femoral hernia (0) Tracheostomy (5) Relaparotomy and ileostomy (6)	Shock (0) Coagulopathy (0) Small bowel leak (6)	Survivor	1	12	1,2	13	27
F	F	35	15	Peritonitis due to ruptured tuboovarian abscess IUCD in-situ	Nil	Posterior culpotomy (−1) Laparotomy, lavage, MM for STAR (0) Laparotomy, reduction of MM (5, 7)	Shock (0) Coagulopathy (0)	Survivor	1	5	1,2	7	29
G	F	76	19	Peritonitis due to perforated sigmoid carcinoma	Hypertension Rheumatoid arthritis	Hartmann's operation (0) Pleural drain (0)	Shock (0) Pneumothorax (0)	Survivor	1	3	1,2	4	15
H	F	68	15	Peritonitis due to perforated sigmoid diverticular abscess	Femoral neck fracture (−2) Previous cervical carcinoma with radiotherapy Peripheral vascular disease	Laparotomy, Hartmann's operation, MM for HIAP (0) Laparotomy, reduction of MM (3) Tracheostomy (4) Laparotomy, removal of MM (5)	Aspiration pneumonitis (0) ARDS (0) Nosocomial *Pseudomonas* pneumonia (5) Systemic candidiasis (7) MRSE bacteraemia (18) Readmission with respiratory failure (23–28)	Survivor	2	11	1,2	20	120
I	M	25	12	Intraabdominal abscess due to idiopathic colonic perforation	NSAID ingestion	Harmann's operation (0)	Shock (0)	Survivor	1	2	1,2	3	12
J	F	72	29	Peritonitis due to perforated ischaemic sigmoid colon	Hypertension Previous transient cerebral ischaemic episodes Beta-adrenergic blockade	Laparotomy, Hartmann's operation, MM for HIAP (0) Laparotomy, reduction of MM (4) Tracheostomy (4) Laparotomy, refashioning of stoma, removal of MM (7)	Shock (0) Coagulopathy (0) *E. coli* wound infection Stomal infarction (7)	Survivor	1	5	1,2,4	9	30

(*continues*)

Table 1. (*continued*) CLINICAL DATA OF 12 PATIENTS WITH PERITONITIS WHO UNDERWENT SEQUENTIAL METABOLIC STUDIES OVER A 21-DAY PERIOD

Patient	Sex	Age (yrs)	Apache II	Septic Source & Etiology	Comorbidity	Surgical Procedures*	Clinical Events*	Outcome*	Prescan (Days)†	Ventilated (Days)	Inotropic Support‡	Days in DCCM	Days in Hospital
K	M	66	21	Peritonitis due to perforated sigmoid diverticulum	CORD	Hartmann's operation (0) Laparotomy, refashioning of colostomy, MM for ease of closure (10) Tracheostomy (10) Laparotomy, removal of MM (22)	Shock (0) ARDS (1) Recurrent AF/SVT Systemic candidiasis (10) Stomal infarction (11) Pneumothorax (14) Peripheral gangrene (23) Abdominal wound fascial dehiscence (26)	Death (28)	4	16	1,2,3	28	28
L	M	68	23	Peritonitis due to leaking anterior resection for carcinoma	IHD Depression	Anterior resection (−6) Anastomosis broken down and end colostomy (0) Laparotomy, MM for HIAP (0) Laparotomy, evacuation of hematoma, abdominal packing, reduction of MM (9) Removal of packing, reduction of MM (10) Tracheostomy (11) Laparotomy, reduction of MM (16) Gastroscopy (24)	Shock (0) HIAP (0) Recurrent atrial flutter ARF (5) Necrosis of abdominal wall (9) Intraabdominal bleeding (9) Gastrointestinal bleeding due to oesophagitis (23)	Survivor	4	19	1,2,5	29	59

DCCM = department of Critical Care Medicine; MM = marlex mesh; HIAP = high intraabdominal pressure; AF = atrial fibrillation; SVT = supraventricular tachycardia; STAR = staged abdominal repair; IHD = ischaemic heart disease; CORD = chronic obstructive respiratory disease.

* Parenthetical figures are days from admission to DCCM.

† Prescan refers to the interval between admission and time of first body compositional analysis (day 0).

‡ 1 = dopamine; 2 = noradrenaline; 3 = adrenaline; 4 = dobutamine; 5 = milrinone.

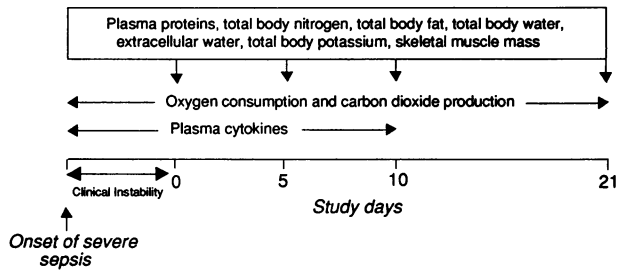

Figure 1. Study design.

Energy balance (kcal) = (ΔTBF × 9.44) + (ΔTBP × 4.704) + (Δtotal body glycogen × 4.18)

where 9.44, 4.704, and 4.18 represent the energy equivalent of the oxidation per gram of fat, protein, and carbohydrate, respectively.[19] Total body glycogen was obtained as described elsewhere[18] from body weight by subtracting TBF, total body water (TBW), TBP, and total minerals, where the latter is the sum of bone mineral content given by dual-energy x-ray absorptiometry (DEXA) and non-bone mineral estimated from TBP.

Total and Activity Energy Expenditure

Total energy intake was calculated from recordings of all nutritional intake, including oral, nasogastric, and nasojejunal intake, intravenous dextrose, and human serum albumin. Total energy expenditure (TEE) was calculated from the difference between this and the energy balance:

TEE (kcal/day) = (total energy intake [kcal]) − energy balance)/days in study

Activity energy expenditure was derived as follows:

Activity energy expenditure (kcal/day) = TEE − REE.

Plasma Proteins

C-reactive protein, prealbumin, and transferrin were measured as markers of the acute-phase response. These were determined by radioimmunodiffusion assay using NOR-Partigen plates (Behringwerke AG, Marburg, Germany).

Cytokines

Blood samples for the determination of plasma cytokine concentrations were collected in 10-ml sterile tubes with lithium heparin anticoagulant and centrifuged within 20 minutes at 1400 g for 5 minutes. The supernatant plasma was separated and frozen at −70°C until analysis. Tumor necrosis factor-alpha (TNFα), interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-1 receptor antagonist (IL-1ra), and soluble 75-kilodalton molecular weight TNF receptor (sTNFR-75) were assayed using sandwich ELISA immunoassays (Quantikine, R&D Systems Ltd., Abingdon, United Kingdom). These assays used microtiter plates, precoated with a specific monoclonal capture antibody and, after incubation with the samples, a specific enzyme-linked polyclonal antibody for detection. A TNFα high-sensitivity kit was also employed, using an amplification system of NADPH/NADH coupled to a secondary enzyme system consisting of alcohol dehydrogenase and diaphorase.

Body Composition

Body weight, total body nitrogen, TBF, TBW, extracellular water (ECW), and total body potassium (TBK) were measured on study days 0, 5, 10, and 21. Body weight was recorded to the nearest 0.1 kg using a hoist weighing system used to transfer the patient from the bed to the body composition scanners.

Total Body Nitrogen

Total body nitrogen was determined using a prompt gamma *in vivo* neutron activation technique in which total body nitrogen is calculated independently of total body hydrogen using a method previously described.[20] The body was scanned twice with a precision of 2.5% and an accuracy, compared with chemical analysis, of within 4% (based on anthropomorphic phantoms).[2] TBP was calculated as 6.25 × total body nitrogen.

Total Body Fat

TBF was measured by DEXA (model DPX+, software version 3.6y, Lunar Radiation Corp., Madison, WI). Using anthropomorphic phantoms of known fat content and with different levels of overhydration, the precision of the technique was 1.3% and the accuracy better than 5%.[2]

Total Body Water

TBW was measured by tritiated water dilution in accordance with previously published methods.[21] Each patient received 3.7 MBq of tritiated water intravenously in 10 ml of sterilized water at the time of each body composition measurement. By analysis of previously reported data,[21] the precision of the method varied from 1.5% when a single sample was taken to 0.9% when three samples (at 4, 5, and 6 hours) were taken. No correction was made for nonaqueous exchangeable hydrogen.

Extracellular and Intracellular Water

ECW was estimated by the dilution of sodium bromide. After an initial blood sample was taken for the basal serum bromide concentration, 50 ml of 5% (w/v) sodium bromide was given intravenously from a syringe that was weighed before and after injection. Samples of blood were taken at 4, 5, and 6 hours after injection, at which time equilibration of sodium bromide in the ECW had occurred. For each patient in the DCCM, a value of the ECW at the time of injection was calculated from the mean of three values derived from the 4-, 5-, and 6-hour serum samples in a manner exactly analogous to the method used for TBW. Patients convalescing in the wards had only a single serum sample taken at 3

hours. The overall mean precision for the measurement of ECW varied from 6.9% when a single sample was taken to 4% when three samples were taken. Bromide was assayed in the serum in accordance with previously published methods.[14]

Intracellular water (ICW) was calculated as the difference between TBW and ECW. The overall mean precision for the measurement of ICW was estimated to vary from 8% when single serum samples were taken for each of TBW and ECW to 4.6% when three samples were taken.

Total Body Potassium

TBK was measured by analysis of the gamma spectrum emitted from naturally occurring K^{40} using a shadow shield counter.[22] The overall precision for a single measurement of TBK was 3%, as determined from replicate measurements of anthropomorphic phantoms with different levels of overhydration (unpublished observations).

A value for intracellular potassium concentration, [K]i, for each study day was calculated as:

$$[K]i\ (mmol/l) = (TBK\ [mmol] - serum\ K\ [mmol/l]) \times ECW\ (l)/ICW\ (l)$$

where serum K is the serum potassium concentration.

Skeletal Muscle Mass

Appendicular skeletal muscle mass was derived from regional analysis of the data obtained by DEXA scanning using the method of Heymsfield et al.[23] Briefly, the fat-free mass (FFM) of the limbs minus the mass of wet bone of the limbs was assumed to approximate limb skeletal muscle mass. Application of the method to critically ill patients requires a correction to the measured FFM[14] to account for the deviation from normal hydration of lean tissue commonly seen in these patients. Total skeletal muscle mass was calculated from appendicular muscle mass by multiplying by 1.25, a factor established from computed tomographic scanning of normal subjects (S.B. Heymsfield, personal communication, 1994). The protein content of total skeletal muscle was assumed to be 17%.[24]

Visceral Mass

Visceral tissue mass was derived from hydration-corrected whole-body FFM by subtracting the masses of wet bone and total skeletal muscle. The protein content of the visceral compartment was derived from TBP by subtracting the protein in skeletal muscle and the protein content of wet bone. The latter was assumed to be 26% of wet bone mass.[24]

Statistical Analysis

Repeated-measures analysis of variance (ANOVA) with asphericity correction was used to detect significant changes over time (SAS Institute, Cary, NC). Student's t test was used when two samples of paired data were compared. In all cases, the 5% level was chosen for statistical significance. Results are expressed as mean ± SEM unless otherwise stated. To satisfy the assumptions of analysis of variance, cytokine and plasma protein measurements were logarithmically transformed before statistical analysis.

RESULTS

Patients

Twelve of the 23 patients who were recruited into the study completed the protocol; their clinical details are listed in Table 1. All 12 had generalized peritonitis secondary to perforation of an abdominal viscus. All underwent urgent surgery and were then treated in our critical care unit. The median time in critical care was 13 days. The median APACHE II score for the 24 hours after admission to the critical care unit was 21.5. Two of the 12 patients died (on days 24 and 28), but the other 10 survived and left the hospital in a median time of 29.5 days. The demographic data, diagnoses, surgical procedures, complications, and outcomes are shown in Table 1. The median time from enrollment to the first scan was 2 days (range 1 to 4 days).

Body Composition Measurements

Table 2 lists the mean ± SEM data for the measurements of body weight, TBF, TBW, ECW, total body nitrogen, skeletal muscle mass, visceral mass, and TBK on days 0, 5, 10, and 21.

Energy Metabolism

Hypermetabolism During the Study Period

Eight of the 12 patients had complete indirect calorimetry measurements of daily REE from 2 days after admission to the DCCM through 12 days, with subsequent measurements 23 days after admission. Figure 2 shows the mean ± SEM daily results and the mean ± SEM predicted REE on study days 0, 5, 10, and 21. Measured REE changed significantly during the study period ($p = 0.014$ by repeated measures ANOVA), rising to a maximum around day 9 after admission, where it averaged 49% higher than predicted. It can be seen from Figure 2 that there were significant elevations in REE on study days 5, 10, and 21. On day 21, REE was still 35% higher than predicted. The extent of elevation of REE above predicted is expected to be underestimated in these patients with fluid overload because of the use of measured body weight in the Harris–Benedict equations.

Total Energy Expenditure and Activity Energy Expenditure

Accurate energy intake was recorded for 8 of the 12 patients between study days 0 and 10. The results of an

Table 2. RESULTS OF BODY COMPOSITION MEASUREMENTS OVER A 21-DAY PERIOD IN 12 PERITONITIS PATIENTS

	Day 0	Day 5	Day 10	Day 21	p*
BW (kg)	79.36 ± 4.69	73.59 ± 4.44†	69.39 ± 4.42‡	66.28 ± 4.32‡	<0.0001
TBF (kg)	17.17 ± 2.23	17.17 ± 2.03	17.12 ± 2.09	16.80 ± 2.00	0.63
TBW (l)	49.12 ± 2.82	43.87 ± 3.12†	40.65 ± 2.72†	38.04 ± 2.65†	<0.0001
ECW (l)	28.16 ± 2.11	24.77 ± 2.05	22.23 ± 1.68†	20.35 ± 2.03	<0.0001
TBN (g)	1482 ± 76	1399 ± 69§	1349 ± 80†	1289 ± 68	<0.0001
SMM (kg)	19.86 ± 1.53	18.58 ± 1.36	16.57 ± 1.23†	16.91 ± 1.45	0.0007
VM (kg)	21.99 ± 1.36	21.53 ± 1.62	20.22 ± 1.80	19.35 ± 1.68	0.049
TBK (mmol)	2979 ± 315	2759 ± 288	2637 ± 252	2428 ± 140	0.014

BW = body weight; TBF = total body fat; TBW = total body water; ECW = extracellular water; TBN = total body nitrogen; SMM = skeletal muscle mass; VM = visceral mass; TBK = total body potassium (5 of the 12 patients had complete TBK measurements).
Values are mean ± standard error of the mean.
* Repeated measures analysis of variance.
† $p < 0.05$.
‡ $p < 0.01$.
§ $p < 0.001$ for paired t test *vs.* preceding measurement.

energy balance calculation for these patients, with estimation of their TEE, are shown in Table 3. The average TEE was 9862 ± 1004 kJ/day (2357 ± 240 kcal/day), which was 1.25 × the average REE during the 10-day period. Energy expended as physical activity during this period was 1992 ± 1017 kJ/day (476 ± 243 kcal/day), making up 20% of the TEE.

Fat Metabolism

For the eight patients who were involved in energy balance studies, Figure 3 shows the relation between the 5-day changes in TBF and the energy deficit calculated by subtracting the energy intake from the TEE. A significant correlation ($r = -0.63$, $p = 0.008$) is seen, showing that fat oxidation occurred in patients whose energy intake was insufficient to achieve energy balance. There is, however, no relation between the quantity of protein administered and the amount of TBP that was hydrolyzed ($r = 0.09$, $p = 0.8$).

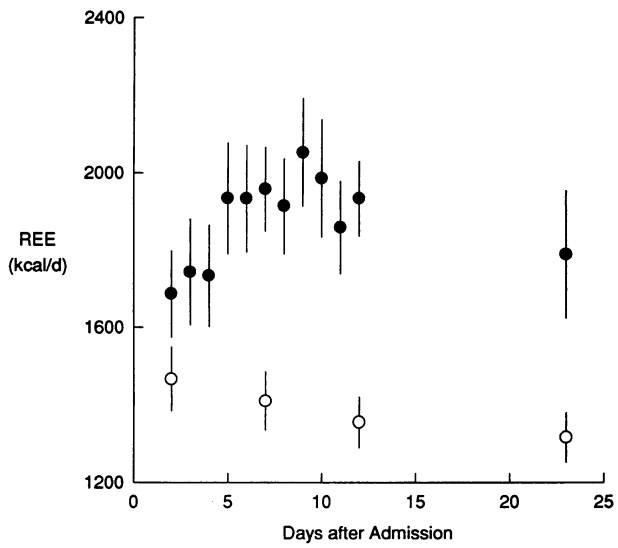

Figure 2. Resting energy expenditure (REE) in eight patients with peritonitis measured for 23 days after onset of sepsis (closed circles), with REE predicted from the Harris–Benedict equation (open circles) (mean ± SEM).

Plasma Proteins and Cytokines

Hepatic Secretory Proteins

The fall in C-reactive protein levels during the study period is shown in Figure 4. C-reactive protein levels were initially high (218.6 mg/l, 95% confidence interval [CI] 157.7 to 303.4 mg/l) but by day 21 had fallen to 27.9 (8.4 to 93) mg/l ($p < 0.001$). Also shown in Figure 4 are prealbumin and transferrin concentrations, which were both initially well below the normal range but rose at a rate consistent with their known turnover rates so that by day 21 they had increased to near-normal levels (prealbumin: 5.9 [95% CI: 4.4 to 8.1] mg/dl to 24.9 [16.2 to 38.5] mg/dl, $p < 0.0001$; transferrin: 69.1 [57.2 to 83.4] mg/dl to 149.8 [108 to 207.6] mg/dl, $p < 0.0001$).

Table 3. ENERGY BALANCE IN EIGHT PERITONITIS PATIENTS MEASURED OVER STUDY DAYS 0 THROUGH 10

Energy intake	2039 ± 56
Energy balance*	−318 ± 264
Total energy expenditure	2357 ± 240
Resting energy expenditure	1881 ± 114
Activity energy expenditure	476 ± 243

Mean ± SEM in kcal/day.
* Sum of the energies of oxidation of protein (−327 ± 65 kcal/day), fat (+216 ± 195 kcal/day) and glycogen (−207 ± 176 kcal/day) gained or lost over the study period.

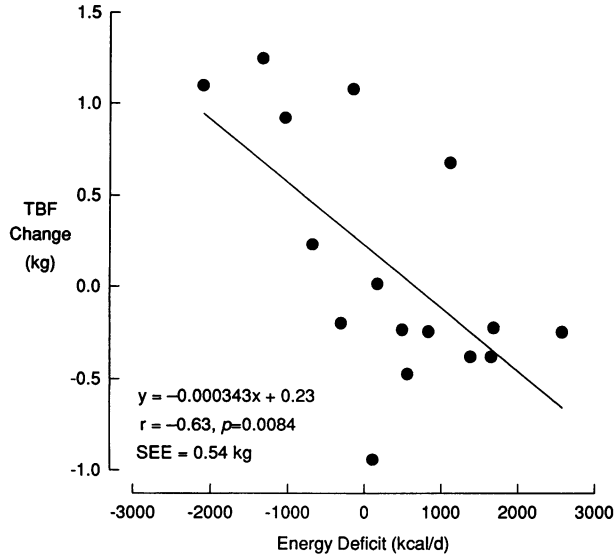

Figure 3. Relation between 5-day changes in total body fat (TBF) and energy deficit in eight patients with peritonitis.

Cytokines

Circulating cytokine and cytokine-antagonist levels over the 12 days after entry to the study are shown in Figure 5 for the 9 patients (A, B, C, D, E, G, H, J, L) for whom cytokine measurements were available. IL-1β was above the detection limit (0.3 pg/ml) in three (H, J, L) of five patients (A, G, H, J, L) with measurements of IL-1β, with concentrations falling rapidly over the first 24 hours (data not shown). TNFα concentrations in these five patients were initially high and were still measurable in all five patients at 12 days. IL-6, IL-8, and IL-10 levels showed similar patterns of change, with initially high concentrations falling rapidly over the first 24 to 48 hours and then declining more slowly out to 12 days. IL-1ra concentrations decreased rapidly over the first 48 hours, followed by a more gradual decline. sTNFR-75 concentrations remained elevated out to 12 days, with an initial drop at 8 hours but with the 96-hour concentration exceeding the initial level.

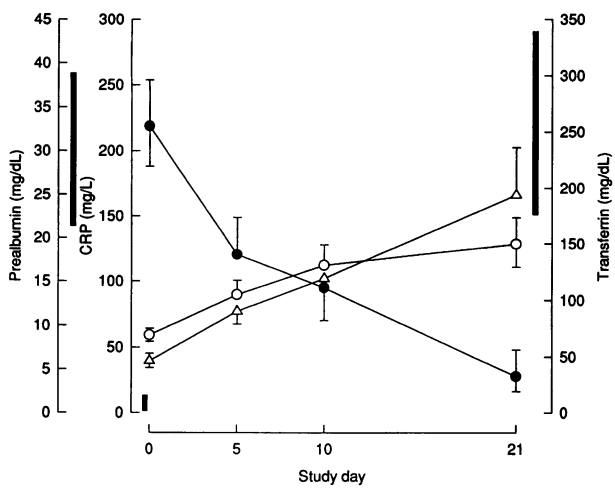

Figure 4. C-reactive protein (CRP, closed circles), prealbumin (triangles), and transferrin (open circles) in 12 patients with peritonitis measured during a 21-day period after onset of sepsis (geometric mean ± SEM). Solid vertical bars indicate normal ranges for these proteins.

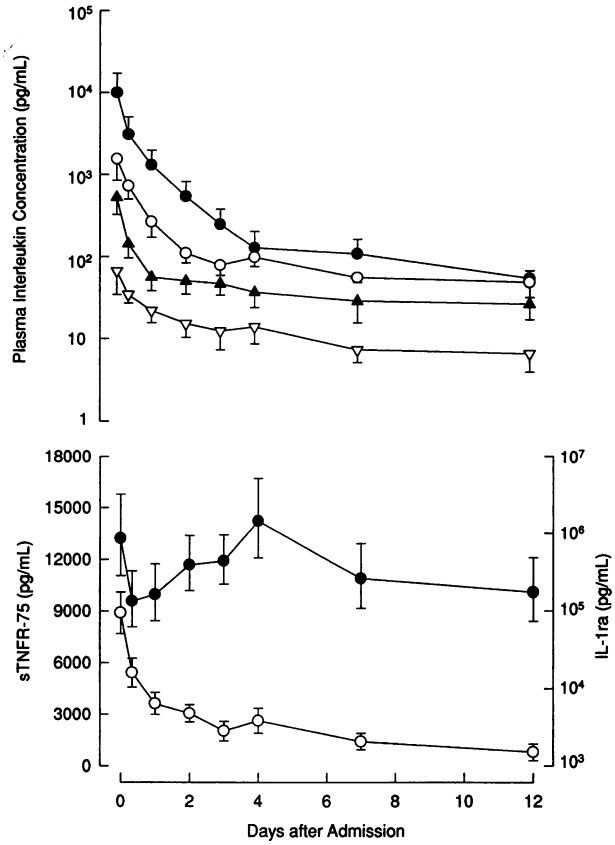

Figure 5. *Upper panel*: Plasma concentrations of IL-6 (closed circles), IL-8 (open circles), and IL-10 (closed triangles) in nine patients with peritonitis and TNFα (open triangles) in five patients with peritonitis, measured during a 12-day period after onset of sepsis (geometric mean ± SEM). *Lower panel*: Plasma concentrations of sTNFR-75 (closed circles) and IL-1ra (open circles) in nine patients with peritonitis measured during a 12-day period after onset of sepsis (geometric mean ± SEM).

Body Weight

Figure 6 shows the changes in body weight that occurred in the group of 12 patients during the 21-day study period. During the period of hemodynamic instability before study day 0, during which time the patients received crystalloids and colloids for resuscitation, there was a positive fluid balance of 12.51 ± 2.37 l. After day 0, when hemodynamic stability had been reached and the patients were receiving nutritional support and maintenance fluids only, the mean weight fell steadily (approximately 0.5 kg/day); preillness weight was reached around day 21. Because there was no change in total body fat mass over the study period (see Table 2), it is clear that the loss of body weight occurred from the FFM.

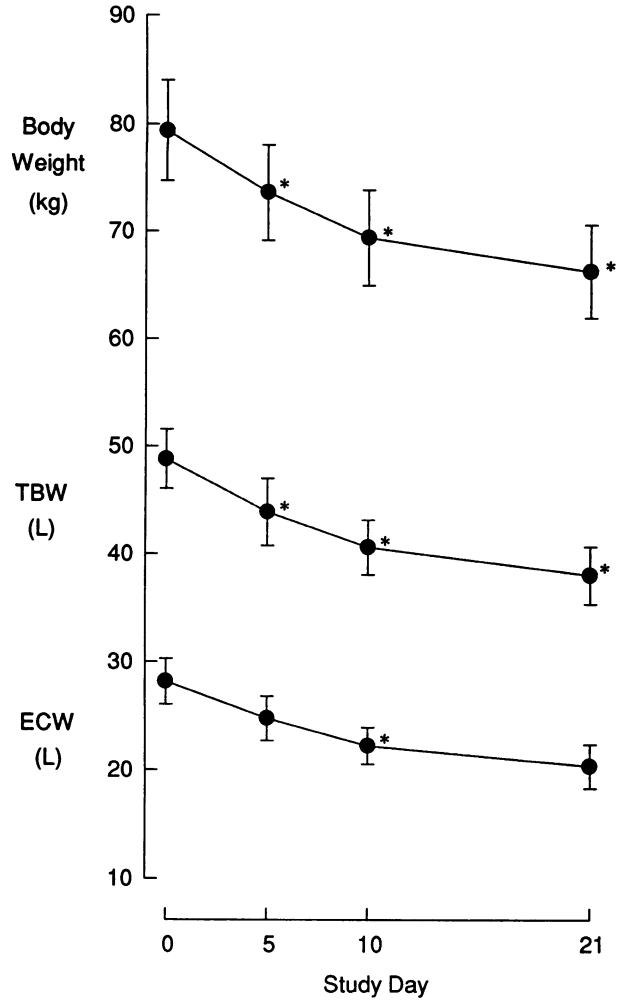

Figure 6. Body weight, total body water (TBW), and extracellular water (ECW) in 12 patients with peritonitis measured during a 21-day period after onset of sepsis (mean ± SEM; * = a significant [$p < 0.05$] change from preceding measurement).

Water Metabolism

Figure 6 also shows the changes in TBW and ECW that occurred during the 21-day study period. Once hemodynamic stability had been reached (day 0), TBW began to return toward normal. By day 21, despite having lost an average of 10.83 ± 1.38 l of water and the mean value of TBW returning to preillness levels, relative overhydration of the FFM was still present (TBW/FFM = 0.77 ± 0.01, which should be compared to normal values of 0.71 and 0.73 for men and women, respectively).[25] Figure 6 shows that most of the TBW changes can be accounted for by changes in ECW, the latter falling by 7.81 ± 1.15 l during the 21-day period ($p < 0.0001$).

Protein Metabolism

Total Body Protein

Figure 7 shows the changes in TBP that occurred during the 21-day study period. The losses were greatest during the first 10 days of the study, amounting to approximately 0.9% of TBP/day. During the 21-day period, a total of 1.21 ± 0.13 kg (13.1%) of TBP was lost ($p < 0.0001$).

Origin of Protein Lost

Figure 7 shows that during the first 10 days of the study, there was an appreciable loss of protein from skeletal muscle in our patients, amounting to 67% of the total protein lost. After this time, the protein loss was predominantly from the nonmuscle tissues. The 0.5-kg loss of skeletal muscle protein during the 21-day study period equates to 42% of the total protein lost during this period.

Cell Composition

Figure 8 shows the changes in TBK, ICW, and [K]i that occurred during the study period in 5 of the 12 patients. During the 21 days of the study, TBK fell significantly ($p = 0.014$), whereas ICW fell slightly ($p=0.039$) and there was no change in [K]i (mean = 131 ± 6 mmol/l). This value is lower than the normal value for our laboratory (152 ± 9 mmol/l, $p = 0.044$),[26] but once hemodynamic stability had been reached, no further deterioration in cellular composition occurred.

DISCUSSION

These results shed new light on the sequential changes in energy, water, fat, and protein metabolism and cell compo-

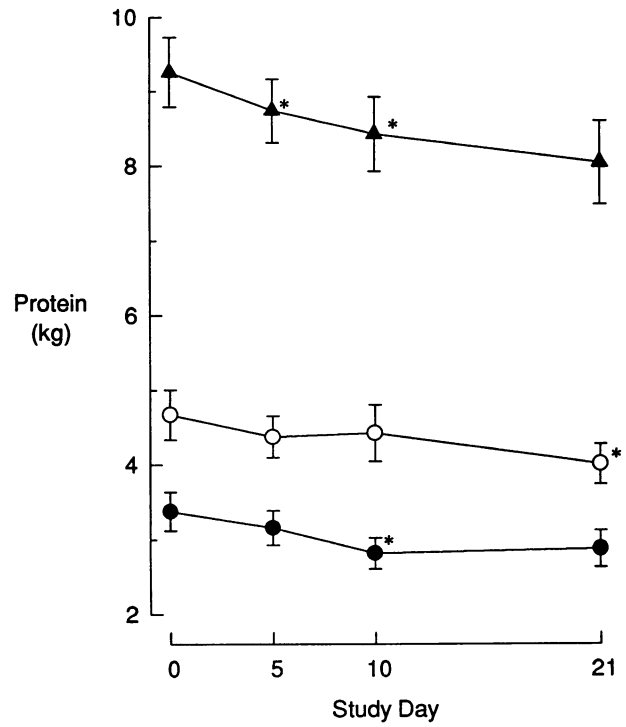

Figure 7. Total body protein (triangles), skeletal muscle protein (closed circles), and visceral protein (open circles) in 12 patients with peritonitis measured during a 21-day period after onset of sepsis (mean ± SEM; * = a significant [$p < 0.05$] change from preceding measurement).

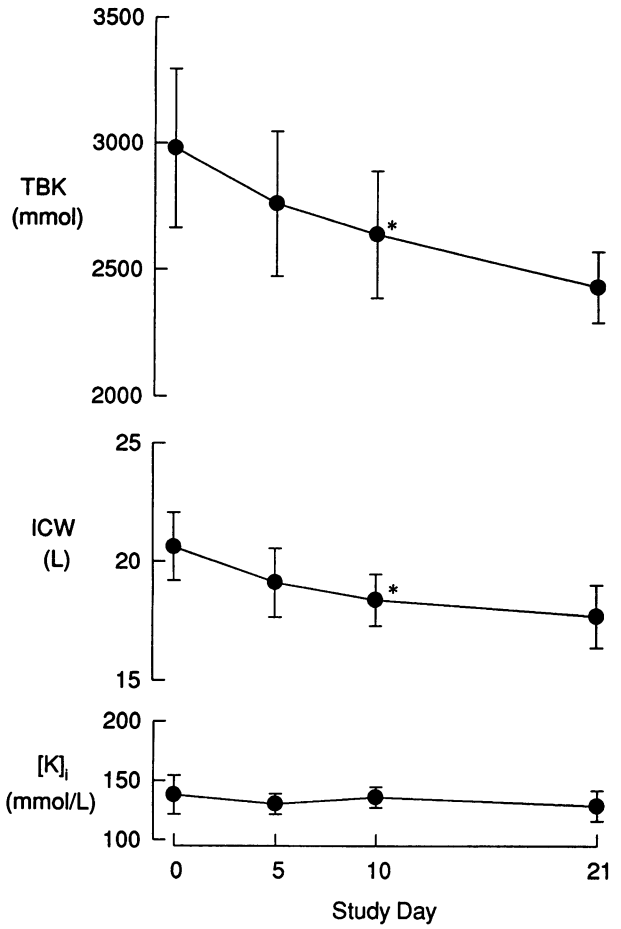

Figure 8. Total body potassium (TBK), intracellular water (ICW), and intracellular potassium concentration ([K]i) in five patients with peritonitis measured during a 21-day period after onset of sepsis (mean ± SEM; * = a significant [$p < 0.05$] change from the day 0 measurement).

sition that occur in patients who are severely septic from peritonitis. There is new information on the cytokine responses as well. The patients in this study each received state-of-the-art surgical and intensive care medical management and as such are generally representative of severely septic patients with peritonitis who are treated in modern surgical units.

Our measurements of REE give values of the same order of magnitude as those described by others,[27–29] although the period of hypermetabolism we found in our patients was prolonged. Because of the formidable problems in measuring TEE and its components in severely septic patients while they are in the critical care unit receiving mechanical ventilation, the energy expended as physical activity is not known. Our results show that activity energy expenditure during the 10 study days averaged 20% of TEE. In clinical practice, total energy requirements are usually calculated by multiplying the measured REE by 1.3.[27] This factor of 1.3 is approximated in the present study, where during a 10-day period, during which an energy balance was conducted, the average TEE was 1.25 × the average measured REE.

It has been suggested that fat oxidation is a major fuel source in severely septic patients,[30–32] but our data show that this is not always so. When energy intake fell short of energy requirements, fat was burned; if energy intake was sufficient or in excess, total body fat stores were preserved or increased.

Our results show once again that there is a reprioritization of hepatic protein synthesis in severe sepsis that is obligatory and independent of changes in TBP. Concentrations of the constitutive plasma proteins fell, and levels of the acute-phase protein, C-reactive protein, rose early in the course of illness. After a few days, as the acute-phase reaction subsided, levels of the constitutive proteins returned to the normal range. These obligatory changes in hepatic protein levels occurred in the face of continuing massive proteolysis and high energy expenditure. There were no correlations between the changes in TBP and those of the constitutive plasma proteins. Our study confirms that measurements of the constitutive plasma proteins have no value in demonstrating changes in TBP early in the course of critical illness.

A few studies have examined circulating cytokine responses in a sequential manner in groups of patients with secondary intraabdominal sepsis.[33–40] For measurements within several hours after surgery, IL-1 was not detectable in every patient,[35–37,39] as observed in the present study. The pattern of changes in TNFα and IL-6 concentrations was broadly similar to the results of the present study. TNFα concentrations fell rapidly over the first 24 hours,[39] whereas IL-6 concentrations remained elevated for 7 days.[35,39] The numbers in our study are too small to identify differences in cytokine responses between survivors and nonsurvivors, as others have done,[33,35,36,39] or to demonstrate significant associations of cytokine concentrations with APACHE II scores.[34,38] No studies that we are aware of have examined changes in IL-10 and the antagonists sTNFR and IL-1ra or changes in IL-8 beyond 8 hours after initial surgery in groups of patients with intraabdominal sepsis. The antiinflammatory cytokine IL-10 was detected in all our patients. Although it is undetectable in healthy volunteers, high levels have been observed in patients with sepsis, particularly those with septic shock.[41–43] Other studies in patients with sepsis have found a response over time similar to our observations, although follow-up has been limited to 3 days.[43] sTNFR-75 concentrations persist at high levels throughout the study period, some 10- to 1000-fold higher than corresponding TNFα concentrations, as observed in other studies of sepsis.[44–46] IL-1ra, the naturally occurring antagonist of IL-1, was detectable in all patients, with initial concentrations three to five orders of magnitude higher than IL-1 in patients with detectable IL-1, as found in the study by Goldie et al.[44]

The patients had retained >12 l of resuscitative fluids by the time they were hemodynamically stable. After this time, body weight began to fall because of the loss of body water, mainly ECW. ICW fell steadily also, but in proportion to the loss of TBK. Cellular composition was abnormal when

measured at the time hemodynamic stability had been reached, and it remained so, but without further deterioration, throughout the study period. Critical illness has been shown to be associated with an alteration in muscle cell composition, as measured by a decrease in skeletal muscle transmembrane potential difference, increased cellular sodium and water levels, and depletion of intracellular potassium and magnesium,[47] so this is not surprising. Perhaps more surprising is the fact that intracellular potassium levels did not fall further in the face of continuing hypermetabolism and proteolysis.

The TBP changes in our patients show the massive losses that occur in association with severe sepsis and show for the first time that early on, most (approximately 70%) of this protein comes from the hydrolysis of skeletal muscle protein. From approximately 12 days after the onset of sepsis, while receiving nutritional support, the patients continued to lose protein, but mainly from tissues other than skeletal muscle, presumably the viscera (see Table 2). The average loss of skeletal muscle mass over the study period was approximately 3 kg, and the loss of visceral mass over the same period was similar. These losses occurred despite state-of-the-art nutritional support.

What are the implications of our findings for modern management of severely septic surgical patients? First, we confirm that the present understanding of the degree of hypermetabolism that occurs in such patients is largely correct, although the surgeons and critical care specialists treating these patients need to understand that this period of hypermetabolism will probably last 3 weeks or longer in most such patients.

Concerning fluid therapy, it is clear from this study that most of the administered resuscitative fluids are retained within the extracellular space. Once hemodynamic stability is reached, body hydration returns to normal, but slowly. It seems unlikely that much can be done to preserve cellular composition before hemodynamic stability is achieved, but state-of-the-art intensive care management appears to have prevented further deterioration. Our work demonstrates that fat oxidation is a function of energy intake; if it is important clinically to preserve fat stores, this can be done by ensuring that total energy requirements are met. Protein losses, which occurred early on from skeletal muscle and later from the viscera, were greater than had been thought in the past. It is likely that this degree of loss profoundly affects muscle function and hence weaning from the ventilator and convalescence. We demonstrated that this protein loss cannot be prevented. In the present study, protein losses were considerable despite close attention to the fluid requirements and nutritional needs of the patients. The cytokine responses demonstrate yet again the complexity, redundancy, and overlap of mediators, suggesting that no single agent or "magic bullet" is likely to modulate the disordered inflammatory process in a clinically significant way.[48]

In conclusion, our study has shown that severe sepsis is associated with hypermetabolism, lipolysis, proteolysis, and extracellular water gain. We have for the first time quantified these changes and shown that they are more prolonged and greater than expected. Overall, these changes are remarkably similar to those that occur in patients after major trauma, although the changes in body water are greater in sepsis.[14] We have also shown that state-of-the-art management can meet energy requirements, prevent lipolysis, and avoid further deterioration in cellular composition. The study further highlights, however, how important it is to focus on research designed to prevent the massive loss of skeletal muscle and visceral protein that occurs.

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